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<b>(54) Title:</b> IMPLANT COMPRISING CALCIUM CEMENT AND HYDROPHOBIC LIQUID  <b>(57) Abstract</b>  The composition comprises a hydraulic cement for implantation in the human or animal body, said hydraulic cement comprising a first component comprising a calcium source and a second component comprising water, which hardens after mixing of the components. The composition further comprises a third component with a hydrophobic liquid. The composition allows to obtain a cement with open macroporosity enabling a rapid bone ingrowth.		

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## IMPLANT COMPRISING CALCIUM CEMENT AND HYDROPHOBIC LIQUID

This invention concerns a composition in accordance with the pre-characterising portion of Claim 1 and a method for producing hardened calcium-containing cement particles or a porous calcium-containing matrix for use in the human or animal body according to the pre-characterising portion of Claim 47.

The porous calcium-containing matrix block or round calcium-containing particles are obtained by combining a calcium-containing hydraulic cement paste with a hydrophobic solution such that (i) the calcium-containing hydraulic cement paste is obtained by mixing one or several powders with an aqueous lubricant; (ii) the lubricant comprises water; (iii) the calcium-containing cement paste hardens with time; (iv) the hydrophobic solution hardly dissolves or do not dissolve in the calcium-containing paste and vice versa; (v) the calcium-containing cement paste and the hydrophobic solution are mixed together to form a so-called emulsion. Depending on the composition of the emulsion, the emulsion is made out of particles of the calcium-containing paste in the hydrophobic solution or out of particles of the hydrophobic solution in the calcium-containing paste; (vi) The mixing of the emulsion is stopped at a given time to obtain either calcium-containing

particles floating in the hydrophobic solution or a calcium-containing matrix having pores filled with the hydrophobic solution.

Calcium phosphates are known to be biocompatible and in most cases osteoconductive. They represent therefore a good alternative to bone grafting. Different forms have been given to calcium phosphates. In most cases, calcium phosphate are sold as granules of about 0,5 to 2,0 mm diameter. Just before implantation, the granules are mixed with the blood of the patient and applied to the desired place. The advantage of this technique is its simplicity and the fact that bone can easily grow in between the granules. However, the granules do not hold together and can migrate away from the defect. For example in the dental area, ceramic granules can migrate out from the gingiva into the mouth which is for obvious reasons not desirable. Furthermore, most commercial granules cannot be easily packed in large amounts in a given defect, because they are not round. Calcium phosphates are also sold as block. On the contrary to granules, blocks can have rather large mechanical properties, but they cannot be shaped according to the bone defect. Furthermore, it is difficult to fabricate a block that has an open-porous structure enabling a rapid bone ingrowth, and when it is the case, the block has low mechanical properties. Another alternative to sell calcium phosphates is as cements. The cements are made of a mixture of one or several calcium phosphate powders and one aqueous solution. Upon mixture with the aqueous solution, the calcium phosphate powders

dissolve and precipitate into another calcium phosphate. Through this precipitation, the paste hardens forming a fine and homogeneous nanoporous or microporous matrix. Such so-called calcium phosphate cements are moldable and injectable, and can have rather large mechanical properties (e.g. more than 100 MPa in compressive strength). However, these cements do not have an open macroporosity enabling a rapid bone ingrowth. In this patent, we are presenting a method and compositions that respond to the problems described above, i.e. enable the obtention of, among others

- a highly-resistant open-macroporous matrix;
- an injectable open-macroporous matrix; or
- round calcium phosphate particles.

The present invention as claimed aims at solving the above described problems.

The present invention provides a cement as defined in Claim 1 and a method for producing hardened calcium-containing cement particles or a porous calcium-containing matrix for use in the human or animal body as defined in Claim 47.

The various features of novelty that characterize the invention are pointed out with particularity in the claims annexed to and forming part of this disclosure. For the better understanding of the invention, its operating advantages and specific objects attained by its use, reference should be made to the accompanying examples in which preferred embodiments of the invention are illustrated in detail.

Further in this description, the use of calcium phosphate hydraulic cement paste will be described. However, calcium sulphate hydraulic cement (gypsum) can also be used and should be therefore included in the calcium phosphate hydraulic cement.

The principle of this invention is to mix a calcium phosphate hydraulic cement paste with a hydrophobic liquid. If the composition of the cement and the hydrophobic liquid are well-chosen, an emulsion is obtained. It can be an emulsion of the cement paste in the hydrophobic liquid or of the hydrophobic liquid in the calcium phosphate paste. If the cement paste hardens in a optimized way, the emulsion can be frozen in its actual structure leading to either a hydrophobic liquid entrapped in a calcium phosphate matrix or calcium phosphate particles or structure floating in a hydrophobic liquid. In the case of a hydrophobic liquid entrapped in a calcium phosphate matrix, the shape, the volume and the interconnectivity of the pores filled with the hydrophobic liquid can be varied depending on the composition of the initial mixture. The possibilities are described herein.

Preferably the hydrophobic liquid is selected from the group of:

ricinoleic acid ( $C_{17}H_{33}O_2$ ), linoleic acid ( $C_{18}H_{32}O_2$ ),  
palmitic acid ( $C_{16}H_{32}O_2$ ), palmitoleic acid ( $C_{17}H_{32}O_2$ ),  
stearic acid ( $C_{18}H_{36}O_2$ ), linolenic acid ( $C_{19}H_{34}O_2$ ),  
arachidic acid ( $C_{20}H_{40}O_2$ ), myristic acid ( $C_{14}H_{28}O_2$ ), lauric

acid ( $C_{11}H_{23}COOH$ ), capric acid ( $C_9H_{19}COOH$ ), caproic acid ( $C_5H_{11}COOH$ ), oleic acid ( $C_{17}H_{33}COOH$ ), caprylic acid ( $C_7H_{15}COOH$ ), erucic acid ( $C_{21}H_{41}COOH$ ), butyric acid ( $C_3H_7COOH$ ), ethyl myristate ( $C_{13}H_{27}COOC_2H_5$ ), ethyl oleate ( $C_{17}H_{33}COOC_2H_5$ ), ethyl palmitate ( $C_{15}H_{31}COOC_2H_5$ ), ethyl linoleate ( $C_{17}H_{31}COOC_2H_5$ ), ethyl laurate ( $C_{11}H_{23}COOC_2H_5$ ), ethyl linolenate ( $C_{17}H_{29}COOC_2H_5$ ), ethyl stearate ( $C_{17}H_{35}COOC_2H_5$ ), ethyl arachidate ( $C_{19}H_{39}COOC_2H_5$ ), ethyl caprilate ( $C_7H_{15}COOC_2H_5$ ), ethyl caprate ( $C_9H_{19}COOC_2H_5$ ), ethyl caproate ( $C_5H_{11}COOC_2H_5$ ), ethyl butyrate ( $C_3H_7COOC_2H_5$ ), triacetin ( $C_9H_{14}O_6$ ), alpha tocopherol ( $C_{29}H_{50}O_2$ ), beta tocopherol ( $C_{28}H_{48}O_2$ ), delta tocopherol ( $C_{27}H_{46}O_2$ ), gamma tocopherol ( $C_{28}H_{48}O_2$ ), benzyl alcohol ( $C_7H_8O$ ), benzyl benzoate ( $C_{14}H_{12}O_2$ ), methylphenol ( $C_7H_8O$ ), di-n-butyl sebacate ( $C_{18}H_{34}O_4$ ), diethylphthalate ( $C_{12}H_{14}O_4$ ), glyceryl monooleate ( $C_{21}H_{40}O_4$ ), lecithin [CAS registry number 8002-43-5], medium chain triglycerides, mineral oil [CAS registry number 8012-95-1], petrolatum [CAS registry number 8009-03-8], and liquid paraffines.

The vegetal oil - as a hydrophobic liquid - is a preferably selected from the group of:

canula oil [no CAS registry number], corn oil [CAS registry number 8001-30-7], cottonseed oil [CAS registry number 8001-29-4], peanut oil [CAS registry number 8002-03-7], sesame oil [CAS registry number 8008-74-0], castor oil [CAS registry number 8001-79-4], and soybean oil [CAS registry number 8001-22-7].

The first component comprises preferably:

calcium sulphate hemihydrate  $[\text{CaSO}_4 \cdot 1/2\text{H}_2\text{O}]$ , calcium pyrophosphate  $[\text{Ca}_2\text{P}_2\text{O}_7]$ , calcium carbonate  $[\text{CaCO}_3]$ , monocalcium phosphate monohydrate  $[\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}]$ , monocalcium phosphate  $[\text{Ca}(\text{H}_2\text{PO}_4)_2]$ , anhydrous dicalcium phosphate  $[\text{CaHPO}_4]$ , dicalcium phosphate dihydrate  $[\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}]$ , octocalcium phosphate  $[\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O}]$ , alpha-tricalcium phosphate  $[\text{alpha-Ca}_3(\text{PO}_4)_2]$ , beta-tricalcium phosphate  $[\text{beta-Ca}_3(\text{PO}_4)_2]$ , hydroxyapatite  $[\text{Ca}_5(\text{PO}_4)_3\text{OH}]$ , tetracalcium phosphate  $[\text{Ca}_4(\text{PO}_4)_2\text{O}]$ , calcium-deficient hydroxyapatite  $[\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}]$ , fluoroapatite  $[\text{Ca}_5(\text{PO}_4)_3\text{F}]$ , amorphous calcium phosphate, oxyapatite  $[\text{Ca}_{10}(\text{PO}_4)_6\text{O}]$ , calcium oxide and calcium hydroxide  $[\text{Ca}(\text{OH})_2]$  or a mixture of some or all of them.

The second component preferably further comprises sulphuric acid  $[\text{H}_2\text{SO}_4]$ , phosphoric acid  $[\text{H}_3\text{PO}_4]$ , citric acid or a mixture of them.

All mixtures and compositions of calcium phosphate cement are possible. Cements with a fast setting time and low initial viscosity are particularly well adapted. Most apatitic cements are more a problem because the hardening reaction may take place very slowly. In the latter case, the hydrophobic liquid has time to coalesce, preventing the obtention of an interconnected porous body. The end product of the cement reaction can vary from dicalcium phosphate dihydrate (Ca/P = 1,0) to calcium deficient hydroxyapatite (Ca/P = 1,33 to



1,67), octocalcium phosphate ( $\text{Ca/P} = 1,33$ ), poorly-crystallized hydroxyapatite ( $\text{Ca/P} = 1,67$ ) or poorly-crystallized carbonatoapatite ( $\text{Ca/P} = 1,7$ ). The cristallinity of the latter phases can vary over a broad range, i.e. from an amorphous phase to a highly-crystalline phase. After sintering (normally above  $800^\circ\text{C}$ ), the end product becomes calcium pyrophosphate, alpha- or beta-TCP, well-crystallized hydroxyapatite, well-crystallized carbonatoapatite, tetracalcium phosphate [ $\text{Ca/P} = 2,0$ ,  $\text{Ca}_4(\text{PO}_4)_2\text{O}$ ] or a mixture of some or all of them.

The particle size distribution and the agglomeration state of the calcium-containing powders determines the setting time of the cement, the volume of the cement mixing liquid needed to obtain a kneadable paste, and the rheological properties of the cement. As a following, the geometrical properties of the starting powders have an important effect on the properties of the final block. In principle, the powders should be non-agglomerated or non-aggregated, round, monodisperse, and small (around 1 micrometer in diameter). The presence of agglomerates or non-spherical particles increases the volume of aqueous solution required to knead the paste, hence increasing the final cement microporosity. The use of a monodisperse powder eases and accelerates the sintering step. The geometrical properties of the powder and in particular the particle size determine the amount of liquid which must be added to the powder to obtain a plastic or a liquid paste. If the particle size is too large, there is no domain where the mixture powder/aqueous solution is plastic. As a following, there is no

possibility to vary the viscosity of the cement paste it is either powdery or liquid. Moreover, the particles tend to sediment in the liquid which is detrimental to the obtention of a homogenous cement paste. With a small mean particle size, the viscosity of the cement paste can be varied over a wide range. However, the powder requires a large amount of mixing liquid is required to obtain a kneadable paste. To obtain an adequate cement paste relative to its rheological properties, its setting time, and its mechanical properties after setting, an optimum must be found. This optimum depends on the application. For example, to obtain a tricalcium phosphate block with an open-porous structure, the use of a mixture of alpha tricalcium phosphate (rather large particle size) and a precipitated tricalcium phosphate (very small particle size) seems to be adequate.

To decrease the viscosity of the cement paste, steric stabilizers can be used. Their purpose is to decrease the interactions between the particles of the cement paste. One example is polyacrylic acid (PAA). This compound adsorbs on alpha-TCP particles in an aqueous solution, reducing the interparticle interactions, and hence decreasing the paste viscosity. The viscosity of a paste made of an aqueous solution and alpha-TCP particles can thus be drastically reduced by using small amounts of PAA (e.g. 1 weight-%). The viscosity can be increased by adding soluble polymers such as polysaccharides, e.g. hydroxypropylmethyl cellulose [CAS registry number 9004-65-3], hydroxypropylmethyl cellulose phthalate [CAS

registry number 9050-31-1], hydroxyethyl cellulose [CAS registry number 9004-62-0], hydroxypropyl cellulose [CAS registry number 9004-64-2], tragacanth gum [CAS registry number 9000-65-1], sodium alginate [CAS registry number 9005-38-3], methyl cellulose [CAS registry number 9004-67-5], xanthan gum [CAS registry number 11138-66-2], hyaluronic acid [CAS registry number 9004-61-9], chitosan [CAS registry number 9012-76-4].

Small amounts (around 1 weight-%) are normally sufficient to reach the desired viscosity increase. The viscosity of the cement paste can also be controlled with the amount of mixing liquid or with the granulometry of the powders. It is clear that the viscosity of the cement paste increases when the amount of mixing liquid decreases. The use of powders with a very small particle size (e.g. 10 to 100 nanometers in diameter) enables the obtention of a very homogeneous and viscous paste.

The cement setting time is of importance. It should be easily controllable and most of the time decreased. This is the case for example for tetracalcium phosphate (TetCP;  $\text{Ca/P} = 2,0$ ,  $\text{Ca}_4(\text{PO}_4)_2\text{O}$ ), dicalcium phosphate dihydrate (DCPD) and water mixtures which have very long setting times (more than an hour). Orthophosphate ions can be added to the aqueous solution leading to a large decrease of the setting time. The latter ions can be added as a salt (e.g. sodium-, potassium-, calcium-, or magnesium orthophosphate) or as an acid (phosphoric acid). Another possibility is to disperse a very fine powder in the cement paste which can act as nucleus for the crystal growth and thus accelerate the precipitation reaction. The powder should

have in principle the same composition and crystal structure as that of the growing crystals. For example, very small hydroxyapatite particles (diameter in the nanometer range) are added to tetracalcium phosphate (TetCP;  $\text{Ca/P} = 2,0$ ,  $\text{Ca}_4(\text{PO}_4)_2\text{O}$ ), dicalcium phosphate dihydrate (DCPD) and water mixtures to decrease the setting time. The same strategy can be used in cements made of alpha-TCP and water. The setting time can be reduced by adding orthophosphate ions (e.g.  $\text{Na}_2\text{HPO}_4$ ,  $\text{KHPO}_4$  or  $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$ ) into the cement formulation (either predissolved in the mixing solution or as solid particles), or by adding small calcium-deficient hydroxyapatite particles into the paste. In other cases, for example beta-TCP/MCPM/water mixtures, the setting time must be slightly increased. This can be done by means of pyrophosphate, citrate or sulphate ions. Actually, all inhibitors of DCPD crystal growth can be used as setting retarder, e.g. phosphocitrate ions, proteins or poly(acrylic acid).

The interfacial energy between the calcium phosphate hydraulic cement paste and the hydrophobic liquid plays an important role in enabling the obtention of an emulsion. A decrease of this interfacial energy is favourable. This decrease can be achieved by using suitable tensioactive agents. These agents have normally an amphipathic character, i.e. have a hydrophobic and a hydrophilic part, such as sodium dodecyl sulphate. Only minute amounts are necessary to reach a good effect (e.g. 0,001 weight-%). The use of a tensioactive agent eases the obtention of an emulsion and allows a good control of the droplet size.

The main requirement for the hydrophobic liquid is to have very little to no mixing with the calcium phosphate hydraulic cement paste. Other factors of importance are the viscosity and the density of the liquid. The viscosity should match that of the calcium phosphate hydraulic cement paste, meaning that the viscosity should reach at least 100 mPa·s. Oils are a good choice. In principle, the problem in the choice of the hydrophobic liquid is that the viscosity of the latter liquid tends to be always too low. Castor oil and canula oil are probably the best choice when it comes to have a readily available, cheap and viscous oil. The density of the liquid must be large enough to prevent a too fast gravimetric phase separation. Values in the range of 0,5 to 5,0 g/ml are probably adequate, preferably close to 1,5 g/ml. The hydrophobic liquid can also be a cement paste in liquid form. Experiments done with polymethylmethacrylate (PMMA) cement have proved to give good results. In that case, the liquid monomer of methylmethacrylate (MMA) and the PMMA powder are initially mixed together and added to the calcium phosphate hydraulic cement paste. Liquid PMMA cement provides a good control of the pore size and volume, and enables (after burning out the hardened cement) the obtention of well-interconnected non-spherical pores in the calcium phosphate cement. However, the monomer of the PMMA cement is toxic and PMMA is not so easy remove. Among all hydrophobic liquids that were tested, the best results were obtained with highly-viscous paraffines and viscous oils such as canula oil and castor oil. As the viscosity of the latter liquids increase with a decrease of temperature, results were better at 4°C than at 25°C.

Other hydrophobic liquids such as Tegosoft M and Triacetin were also tested. But both solutions have a rather low viscosity which prevents a good mixing with the cement. However, both are accepted for parenteral applications, implying that an injectable paste could be developed which could harden in vivo and have interconnected macropores.

It is of importance to control the size, the volume and the interconnectivity of the macropores in order to obtain an open macroporous calcium phosphate matrix. The volume can be controlled by the amount of hydrophobic liquid added to the calcium phosphate hydraulic cement paste. It can also be controlled by the addition of granules that can be dissolved or burned after cement hardening. The macropore size depends on the volume of hydrophobic liquid added to the cement paste. Normally, the larger this volume the larger the macropores. However, the use of tensioactive agents enables a good control of the macropore size. The macropore interconnectivity is related to the volume and the size of the macropores. The use of a tensioactive agent has a tendency to decrease the interconnectivity. A decrease of the viscosity of the hydrophilic/hydrophobic mixture has also a tendency to decrease the interconnectivity. The best way to get interconnected macropores is to have a mixture that sets very quickly, hence freezing the structure, and/or to have a rather viscous mixture. A favourable condition is to take a calcium phosphate hydraulic cement paste

which has a viscosity at the limit between a plastic and a liquid state or which is thixotrope, i.e. has a viscosity decreasing with an increase in shear stresses.

After hardening, the calcium phosphate hydraulic cement paste has a rather high micro- or even nanoporosity. This volume can range from 25 - 30 volume-% to 80 volume-%. This volume depends on the amount of mixing liquid added to the calcium phosphate powders. The micropore volume can be reduced by sintering the calcium phosphate matrix. If the sintering conditions are well adjusted, the microporous volume should be close to 0 %.

In a preferred embodiment of the invention the hydrophobic liquid can be added in two or more steps. By this method a first emulsion ("hydrophobic liquid in cement paste") is made and subsequently an "emulsion of the emulsion" is made by diluting the first emulsion into additional hydrophobic liquid. Such a double emulsion with water may be called a "water in oil in water double emulsion process".

#### Example 1

8 g alpha-TCP, 1,2 g precipitated tricalcium phosphate, (this tricalcium phosphate is a calcium-deficient hydroxyapatite with the chemical composition  $\text{Ca}_9(\text{HPO}_4)(\text{PO}_4)_5\text{OH}$ ; it is obtained by precipitation and is transformed into beta-TCP above 500-600°C), 5,0 ml of a PAA 1 % and Cremophor EL (polyethoxylated castor oil) 0,001 % solution and 8,0 ml paraffine are mixed together

for 4 minutes. The mixture is then poured into a mold and left to harden. After 12 hours, the hardened mixture is unmolded and left in water for 2 subsequent days to complete setting reaction. The sample is then sintered at 1250 °C for 4 hours. The composition of the final sample is beta-TCP. The sample has nice and large interconnected macropores. The overall porosity is 75 %, 55 % of pores being in the range of  $200 < d < 500$  microns and 18 % of pores being in the range of  $0,05 < d < 10$  microns. The 2 remaining percents are not comprised in these two ranges. The interconnections have a diameter in the range of 100 to 300 microns.

#### Example 2

1,1 g beta-TCP, 0,9 g MCPM, 0,02 g  $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$ , 0,8 ml  $\text{H}_2\text{O}$ , and 100 ml canula oil are stirred together for 10 minutes. The mixture is filtered and the granules - generated by the hardening of the hydraulic cement mixture - collected on the filter paper are sintered at 1100°C for 2 hours. The granules collected after sintering are round, monodisperse and dense. They have a diameter in the range of 100 to 300 microns. The granules are made out of almost pure calcium pyrophosphate.

#### Example 3

8 g  $\alpha$ -TCP, 0,8 g precipitated tricalcium phosphate, 0,5 g CC, 6,0 ml of Cremophor EL 0,001 % solution, and 8,0 ml Tegosoft M (isopropyl myristate  $\text{C}_{17}\text{H}_{34}\text{O}_2$ ) are mixed together for 4 minutes. The mixture is then poured into a syringe and injected into a cavity. After hardening, the cavity is filled with an open



macroporous calcium phosphate structure. As shown by x-ray diffraction and FTIR analysis, the calcium phosphate is a poorly-crystallized calcium-deficient carbonated hydroxyapatite.

**Claims**

1. Composition comprising a hydraulic cement for implantation in the human or animal body, said hydraulic cement comprising a first component comprising a calcium source and a second component comprising water, which hardens after mixing of the components,

**characterized in that**

it further comprises a third component with a hydrophobic liquid.

2. Composition according to claim 1, characterized in that the hydrophobic liquid is selected from the group of

ricinoleic acid ( $C_{17}H_{33}O_2COOH$ ), linoleic acid ( $C_{17}H_{31}COOH$ ), palmitic acid ( $C_{15}H_{31}COOH$ ), palmitoleic acid ( $C_{15}H_{29}COOH$ ), stearic acid ( $C_{17}H_{35}COOH$ ), linolenic acid ( $C_{17}H_{29}COOH$ ), arachidic acid ( $C_{19}H_{39}COOH$ ), myristic acid ( $C_{13}H_{27}COOH$ ), lauric acid ( $C_{11}H_{23}COOH$ ), capric acid ( $C_9H_{19}COOH$ ), caproic acid ( $C_5H_{11}COOH$ ), oleic acid ( $C_{17}H_{33}COOH$ ), caprylic acid ( $C_7H_{15}COOH$ ), erucic acid ( $C_{21}H_{41}COOH$ ), butyric acid ( $C_3H_7COOH$ ), ethyl myristate ( $C_{13}H_{27}COOC_2H_5$ ), ethyl oleate ( $C_{17}H_{33}COOC_2H_5$ ), ethyl palmitate ( $C_{15}H_{31}COOC_2H_5$ ), ethyl linoleate ( $C_{17}H_{31}COOC_2H_5$ ), ethyl laurate ( $C_{11}H_{23}COOC_2H_5$ ), ethyl linolenate ( $C_{17}H_{29}COOC_2H_5$ ), ethyl stearate ( $C_{17}H_{35}COOC_2H_5$ ), ethyl arachidate ( $C_{19}H_{39}COOC_2H_5$ ), ethyl caprilate ( $C_7H_{15}COOC_2H_5$ ), ethyl caprate ( $C_9H_{19}COOC_2H_5$ ), ethyl caproate ( $C_5H_{11}COOC_2H_5$ ), ethyl butyrate ( $C_3H_7COOC_2H_5$ ), triacetin ( $C_9H_{14}O_6$ ), alpha tocopherol ( $C_{29}H_{50}O_2$ ), beta tocopherol ( $C_{28}H_{48}O_2$ ), delta tocopherol ( $C_{27}H_{46}O_2$ ), gamma

tocopherol ( $C_{28}H_{48}O_2$ ), benzyl alcohol ( $C_7H_8O$ ), benzyl benzoate ( $C_{14}H_{12}O_2$ ), methylphenol ( $C_7H_8O$ ), di-n-butyl sebacate ( $C_{18}H_{34}O_4$ ), diethylphthalate ( $C_{12}H_{14}O_4$ ), glyceryl monooleate ( $C_{21}H_{40}O_4$ ), lecithin, medium chain triglycerides, mineral oil, petrolatum, and liquid paraffines.

3. Composition according to claim 1, characterized in that the hydrophobic liquid is a vegetal oil preferably selected from the group of:

canula oil, corn oil, cottonseed oil, peanut oil, sesame oil, castor oil, and soybean oil.

4. Composition according to one of the claims 1 to 3, characterized in that said first and second component correspond together to 0,001 to 90,000 volume-% of the total weight of the three components together.

5. Composition according to claim 4, characterized in that said first and second component correspond together to 0,1 to 80,0 volume-% of the total weight of the three components together.

6. Composition according to one of the claims 1 to 5, characterized in that said third component corresponds to 10 to 90 volume-% of the total weight of the three components together.

7. Composition according to claim 6, characterized in that said third component corresponds to 20 to 80 volume-% of the total weight of the three components together.

8. Composition according to one of the claims 1 to 7, characterized in that it is obtained by combining 40 to 70 volume-% of said first and second component with 30 to 60 volume-% of said third component.

9. Composition according to one of the claims 1 to 8, characterized in that it has a CaP molar ratio comprised between 1,0 and 20,0.

10. Composition according to claim 9, characterized in that it has a CaP molar ratio comprised between 1,0 and 2,0.

11. Composition according to claim 10, characterized in that the calcium-containing cement paste has a CaP molar ratio comprised between 1,0 to 1,67.

12. Composition according to claim 11, characterized in that the calcium-containing cement paste has a CaP molar ratio comprised between 1,45 to 1,60.

13. Composition according to one of the claims 1 to 12, characterized in that said first component comprises calcium sulphate hemihydrate  $[\text{CaSO}_4 \cdot 1/2\text{H}_2\text{O}]$ , calcium pyrophosphate  $[\text{Ca}_2\text{P}_2\text{O}_7]$ , calcium carbonate  $[\text{CaCO}_3]$ , monocalcium phosphate

monohydrate  $[\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}]$ , monocalcium phosphate  
 $[\text{Ca}(\text{H}_2\text{PO}_4)_2]$ , anhydrous dicalcium phosphate  $[\text{CaHPO}_4]$ , dicalcium  
phosphate dihydrate  $[\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}]$ , octocalcium phosphate  
 $[\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O}]$ , alpha-tricalcium phosphate  
 $[\text{alpha-Ca}_3(\text{PO}_4)_2]$ , beta-tricalcium phosphate  $[\text{beta-Ca}_3(\text{PO}_4)_2]$ ,  
hydroxyapatite  $[\text{Ca}_5(\text{PO}_4)_3\text{OH}]$ , tetracalcium phosphate  
 $[\text{Ca}_4(\text{PO}_4)_2\text{O}]$ , calcium-deficient hydroxyapatite  
 $[\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}]$ , fluoroapatite  $[\text{Ca}_5(\text{PO}_4)_3\text{F}]$ ,  
amorphous calcium phosphate, oxyapatite  $[\text{Ca}_{10}(\text{PO}_4)_6\text{O}]$ , calcium  
oxide and calcium hydroxide  $[\text{Ca}(\text{OH})_2]$  or a mixture of some or all  
of them.

14. Composition according to one of the claims 1 to 13,  
characterized in that said second component further comprises  
sulphuric acid  $[\text{H}_2\text{SO}_4]$ , phosphoric acid  $[\text{H}_3\text{PO}_4]$ , citric acid or  
a mixture of them.

15. Composition according to one of the claims 1 to 14,  
characterized in that said second component further comprises an  
additive to control the cement setting time, said additive being  
either a liquid substance or a solid substance soluble in water.

16. Composition according to claim 15, characterized in that  
said additive comprises a substance chosen from the group of  
pyrophosphate, citrate, magnesium, orthophosphate or  
polyphosphate ions, amino acids, peptides or proteins.

17. Composition according to one of the claims 1 to 16, characterized in that said second component further comprises an additive to control the cement rheology, preferably a polymer.

18. Composition according to claim 17, characterized in that said polymer is a polysaccharide.

19. Composition according to claim 18, characterized in that said polysaccharide is chosen from the group of:

hydroxypropylmethyl cellulose [CAS registry number 9004-65-3], hydroxypropylmethyl cellulose phthalate [CAS registry number 9050-31-1], hydroxyethyl cellulose [CAS registry number 9004-62-0], hydroxypropyl cellulose [CAS registry number 9004-64-2], tragacanth gum [CAS registry number 9000-65-1], sodium alginate [CAS registry number 9005-38-3], methyl cellulose [CAS registry number 9004-67-5], xanthan gum [CAS registry number 11138-66-2], hyaluronic acid [CAS registry number 9004-61-9], chitosan [CAS registry number 9012-76-4].

20. Composition according to claim 17, characterized in that said polymer is chosen from the group of:  
polyvinyl alcohol or propylene glycol alginate.

21. Composition according to one of the claims 1 to 20, characterized in that the hydrophobic forms an emulsion with the first and second component of said hydraulic cement.

22. Composition according to one of the claims 1 to 21, characterized in that said second component further comprises a surfactant or emulsifier to accelerate and stabilize the formation of an emulsion.

23. Composition according to claim 22, characterized in that said surfactant or emulsifier is selected from the group of:

docusate sodium ( $C_{20}H_{37}NaO_7S$ ), sodium lauryl sulfate ( $C_{12}H_{25}NaO_4S$ ), stearic acid ( $C_{17}H_{35}COOH$ ), alkyldimethyl(phenylmethyl)ammonium chloride [CAS registry number 8001-54-5], benzethonium chloride ( $C_{27}H_{42}ClNO_2$ ), cetrimide ( $C_{17}H_{38}BrN$ ), glycerin monooleate ( $C_{21}H_{40}O_4$ ), polysorbate 20 ( $C_{58}H_{114}O_{26}$ ), polysorbate 21 ( $C_{26}H_{50}O_{10}$ ), polysorbate 40 ( $C_{62}H_{122}O_{26}$ ), polysorbate 60 ( $C_{64}H_{126}O_{26}$ ), polysorbate 61 ( $C_{32}H_{62}O_{10}$ ), polysorbate 65 ( $C_{100}H_{194}O_{28}$ ), polysorbate 80 ( $C_{64}H_{124}O_{26}$ ), polysorbate 81 ( $C_{34}H_{64}O_{11}$ ), polysorbate 85 ( $C_{100}H_{188}O_{28}$ ), polysorbate 120 ( $C_{64}H_{126}O_{26}$ ), polyvinyl alcohol ( $(C_2H_4O)_n$ ), sorbitan di-isostearate ( $C_{42}H_{80}O_7$ ), sorbitan dioleate ( $C_{42}H_{76}O_7$ ), sorbitan monoisostearate ( $C_{24}H_{46}O_6$ ), sorbitan monolaurate ( $C_{18}H_{34}O_6$ ), sorbitan monooleate ( $C_{24}H_{44}O_6$ ), sorbitan monopalmitate ( $C_{22}H_{42}O_6$ ), sorbitan monostearate ( $C_{24}H_{46}O_6$ ), sorbitan sesqui-isostearate ( $C_{33}H_{63}O_{6.5}$ ), sorbitan sesquioleate ( $C_{33}H_{63}O_{6.5}$ ), sorbitan sesquistearate ( $C_{33}H_{63}O_{6.5}$ ), sorbitan tri-isostearate ( $C_{33}H_{63}O_{6.5}$ ), sorbitan trioleate ( $C_{33}H_{63}O_{6.5}$ ), sorbitan tristearate ( $C_{33}H_{63}O_{6.5}$ ), glyceryl monooleate ( $C_{21}H_{40}O_4$ ), isopropyl myristate ( $C_{17}H_{34}O_2$ ), isopropyl palmitate

( $C_{19}H_{38}O_2$ ), lanolin [CAS registry number 8006-54-0], lanolin alcohols [CAS registry number 8027-33-6], hydrous lanolin [CAS registry number 8020-84-6], lecithin [CAS registry number 8002-43-5], medium chain triglycerides (no registry number), monoethanolamine ( $C_2H_7NO$ ), oleic acid ( $C_{17}H_{33}COOH$ ), polyethylene glycol monocetyl ether [CAS registry number 9004-95-9], polyethylene glycol monostearyl ether [CAS registry number 9005-00-9], polyethylene glycol monolauryl ether [CAS registry number 9002-92-0], polyethylene glycol monooleyl ether [CAS registry number 9004-98-2], polyethoxylated castor oil [CAS registry number 61791-12-6], polyoxyl 40 stearate ( $C_{98}H_{196}O_{42}$ ), polyoxyl 50 stearate ( $C_{118}H_{236}O_{52}$ ), triethanolamine ( $C_6H_{15}NO_3$ ), anionic emulsifying wax [CAS registry number 8014-38-8], nonionic emulsifying wax [CAS registry number 977069-99-0], and sodium dodecyl sulphate ( $NaC_{12}H_{25}SO_4$ ).

24. Composition according to one of the claims 1 to 23, characterized in that said second component further comprises a polymer to sterically stabilize the first component, preferably polyacrylic acid.

25. Composition according to claim 24, characterized in that said polymer is a polyacrylic acid.

26. Composition according to one of the claims 1 to 25, characterized in that the setting time of the cement upon mixing of said three components is comprised between 1 and 600 minutes.



27. Composition according to claim 26, characterized in that said setting time is between 2 and 60 minutes.

28. Composition according to claim 27, characterized in that setting time is comprised between 5 and 20 minutes.

29. Composition according to one of the claims 1 to 28, characterized in that the volume of the second component VL of the cement is in the range of  $0,5 \text{ VT} < \text{VL} < 10 \text{ VT}$  where VT is the volume of the first component.

30. Composition according to one of the claims 1 to 29, characterized in that the volume of the second component VL of the cement is in the range of  $0,8 \text{ VT} < \text{VL} < 2,0 \text{ VT}$  where VT is the volume of the first component.

31. Composition according to one of the claims 1 to 30, characterized in that the third component has a viscosity SHS comprised between  $0,01 \text{ SC} < \text{SHS} < 100,00 \text{ SC}$  where SC is the viscosity of the mixture resulting from the first and second component.

32. Composition according to one of the claims 1 to 31, characterized in that the hydrophobic substance has a viscosity comprised between 0,01 and 100'000 mPa·s at a temperature comprised in the range of 0°C to 55°C.

33. Composition according to one of the claims 1 to 32, characterized in that the hydrophobic substance has a density comprised between 0,2 and 10,0 g/cm<sup>3</sup>.

34. Composition according to one of the claims 1 to 33, characterized in that it may further comprise granules whose diameter is at least two times, preferably at least 10 times larger than the average diameter of the particles of the first component.

35. Composition according to one of the claims 1 to 34, characterized in that the granules have an average diameter in the range of 1 mm to 3 mm.

36. Composition according to claim 34 or 35, characterized in that the granules are made out of calcium phosphate.

37. Composition according to claim 34 or 35, characterized in that the granules are made out of polymer.

38. Composition according to claim 34 or 35, characterized in that the granules are made out of bioglass.

39. Composition according to one of the claims 1 to 38, characterized in that the hardened cement paste comprises calcium-deficient hydroxyapatite  $[\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}]$  with  $0 \leq x \leq 2$ .

40. Composition according to one of the claims 1 to 38, characterized in that the hardened cement paste comprises dicalcium phosphate dihydrate  $[\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}]$ .

41. Composition according to one of the claims 1 to 40, characterized in that the first component comprises beta-tricalcium phosphate and a further substance selected from the group of monocalcium phosphate monohydrate  $[\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}]$  or monocalcium phosphate  $[\text{Ca}(\text{H}_2\text{PO}_4)_2]$  or phosphoric acid  $[\text{H}_3\text{PO}_4]$ .

42. Composition according to one of the claims 1 to 40, characterized in that the first component comprises alpha-tricalcium phosphate.

43. Composition according to claim 42, characterized in that the first component further comprises a precipitated calcium phosphate.

44. Composition according to claim 43, characterized in that said precipitated calcium phosphate has a Ca/P molar ratio of  $1,50 \pm 0,02$ .

45. Composition according to one of the claims 1 to 44, characterized in that the mixture comprises pharmaceutically or physiologically active substances, preferably antibiotics, anti-inflammatory drugs, peptides, and proteins.

[those drugs which are hydrophilic are added to the second component, those which are hydrophobic to the third]

46. Composition according to one of the claims 1 to 45, characterized in that the hydrophobic liquid is an autopolymerizable cement which hardens with time, preferably based on methacrylate.

47. Method for producing hardened calcium-containing cement particles or a porous calcium-containing matrix for use in the human or animal body,

**characterized in that**

A) a hydrophobic liquid is added to a freshly mixed calcium-containing hydraulic cement paste or prior to mixing to one of its components

B) the components of step A) are mixed in order to form an emulsion such as the hydrophobic liquid is made out of particles of the calcium-containing hydraulic cement paste in the hydrophobic liquid or out of particles of the hydrophobic liquid in the calcium-containing hydraulic cement paste,

C) the mixing of the emulsion is stopped at a given time to obtain either hardened calcium-containing cement particles floating in the hydrophobic liquid or a hardened calcium-containing matrix having pores filled with the hydrophobic liquid.

48. Method according to claim 47, characterized in that the said hardened calcium-containing cement particles are filtered from the hydrophobic liquid to produce an implantable granulate of calcium-containing hydraulic cement particles.

49. Method according to claim 47 or 48, characterized in that said hydrophobic liquid is added in several steps to said freshly mixed calcium-containing hydraulic cement paste.

50. Method according to one of the claims 47 to 49, characterized in that the hydrophobic liquid is removed from the hardened cement mixture, preferably by washing, freeze-drying, evaporation, thermolysis or a combination of these procedures.

51. Method according to one of the claims 47 to 50, characterized in that the hardened cement mixture is sintered.

52. Open macroporous block of beta-tricalcium phosphate obtained by a method according to one of the claims 47 to 51.

**AMENDED CLAIMS**

[received by the International Bureau on 16 November 1999 (16.11.99);  
original claims 1-23 amended;  
remaining claims unchanged (7 pages)]

1. Composition comprising a hydraulic cement for implantation in the human or animal body, said hydraulic cement comprising a first component comprising a calcium source, a second component comprising water, which hardens after mixing of the components and a third component comprising a hydrophobic liquid, characterized in that the hydrophobic liquid of the third component is able to form an emulsion with the first and second component of said hydraulic cement.

2. Composition according to claim 1, characterized in that said second component further comprises a surfactant or emulsifier to accelerate and stabilize the formation of an emulsion.

3. Composition according to claim 2, characterized in that said surfactant or emulsifier is selected from the group of:

docusate sodium ( $C_{20}H_{37}NaO_7S$ ), sodium lauryl sulfate ( $C_{12}H_{25}NaO_4S$ ), stearic acid ( $C_{17}H_{35}COOH$ ), alkyldimethyl(phenylmethyl)ammonium chloride [CAS registry number 8001-54-5], benzethonium chloride ( $C_{27}H_{42}ClNO_2$ ), cetrimide ( $C_{17}H_{38}BrN$ ), glycerin monooleate ( $C_{21}H_{40}O_4$ ), polysorbate 20 ( $C_{58}H_{114}O_{26}$ ), polysorbate 21 ( $C_{26}H_{50}O_{10}$ ), polysorbate 40 ( $C_{62}H_{122}O_{26}$ ), polysorbate 60 ( $C_{64}H_{126}O_{26}$ ), polysorbate 61 ( $C_{32}H_{62}O_{10}$ ), polysorbate 65 ( $C_{100}H_{194}O_{28}$ ), polysorbate 80 ( $C_{64}H_{124}O_{26}$ ), polysorbate 81 ( $C_{34}H_{64}O_{11}$ ), polysorbate 85 ( $C_{100}H_{188}O_{28}$ ), polysorbate 120 ( $C_{64}H_{126}O_{26}$ ), polyvinyl alcohol ( $(C_2H_4O)_n$ ), sorbitan di-isostearate

(C<sub>42</sub>H<sub>80</sub>O<sub>7</sub>), sorbitan dioleate (C<sub>42</sub>H<sub>76</sub>O<sub>7</sub>), sorbitan monoisostearate (C<sub>24</sub>H<sub>46</sub>O<sub>6</sub>), sorbitan monolaurate (C<sub>18</sub>H<sub>34</sub>O<sub>6</sub>), sorbitan monooleate (C<sub>24</sub>H<sub>44</sub>O<sub>6</sub>), sorbitan monopalmitate (C<sub>22</sub>H<sub>42</sub>O<sub>6</sub>), sorbitan monostearate (C<sub>24</sub>H<sub>46</sub>O<sub>6</sub>), sorbitan sesqui-isostearate (C<sub>33</sub>H<sub>63</sub>O<sub>6.5</sub>), sorbitan sesquioleate (C<sub>33</sub>H<sub>63</sub>O<sub>6.5</sub>), sorbitan sesquistearate (C<sub>33</sub>H<sub>63</sub>O<sub>6.5</sub>), sorbitan tri-isostearate (C<sub>33</sub>H<sub>63</sub>O<sub>6.5</sub>), sorbitan trioleate (C<sub>33</sub>H<sub>63</sub>O<sub>6.5</sub>), sorbitan tristearate (C<sub>33</sub>H<sub>63</sub>O<sub>6.5</sub>), glyceryl monooleate (C<sub>21</sub>H<sub>40</sub>O<sub>4</sub>), isopropyl myristate (C<sub>17</sub>H<sub>34</sub>O<sub>2</sub>), isopropyl palmitate (C<sub>19</sub>H<sub>38</sub>O<sub>2</sub>), lanolin [CAS registry number 8006-54-0], lanolin alcohols [CAS registry number 8027-33-6], hydrous lanolin [CAS registry number 8020-84-6], lecithin [CAS registry number 8002-43-5], medium chain triglycerides (no registry number), monoethanolamine (C<sub>2</sub>H<sub>7</sub>NO), oleic acid (C<sub>17</sub>H<sub>33</sub>COOH), polyethylene glycol monocetyl ether [CAS registry number 9004-95-9], polyethylene glycol monostearyl ether [CAS registry number 9005-00-9], polyethylene glycol monolauryl ether [CAS registry number 9002-92-0], polyethylene glycol monooleyl ether [CAS registry number 9004-98-2], polyethoxylated castor oil [CAS registry number 61791-12-6], polyoxyl 40 stearate (C<sub>98</sub>H<sub>196</sub>O<sub>42</sub>), polyoxyl 50 stearate (C<sub>118</sub>H<sub>236</sub>O<sub>52</sub>), triethanolamine (C<sub>6</sub>H<sub>15</sub>NO<sub>3</sub>), anionic emulsifying wax [CAS registry number 8014-38-8], nonionic emulsifying wax [CAS registry number 977069-99-0], and sodium dodecyl sulphate (NaC<sub>12</sub>H<sub>25</sub>SO<sub>4</sub>).

4. Composition according to one of the claims 1 to 3, characterized in that the hydrophobic liquid is selected from the group of

ricinoleic acid ( $C_{17}H_{33}O_2$ ), linoleic acid ( $C_{18}H_{32}O_2$ ), palmitic acid ( $C_{16}H_{32}O_2$ ), palmitoleic acid ( $C_{17}H_{32}O_2$ ), stearic acid ( $C_{18}H_{36}O_2$ ), linolenic acid ( $C_{18}H_{32}O_2$ ), arachidic acid ( $C_{20}H_{40}O_2$ ), myristic acid ( $C_{14}H_{28}O_2$ ), lauric acid ( $C_{12}H_{24}O_2$ ), capric acid ( $C_{10}H_{20}O_2$ ), caproic acid ( $C_8H_{16}O_2$ ), oleic acid ( $C_{18}H_{34}O_2$ ), caprylic acid ( $C_8H_{16}O_2$ ), erucic acid ( $C_{22}H_{42}O_2$ ), butyric acid ( $C_4H_8O_2$ ), ethyl myristate ( $C_{18}H_{36}O_2$ ), ethyl oleate ( $C_{19}H_{38}O_2$ ), ethyl palmitate ( $C_{20}H_{40}O_2$ ), ethyl linoleate ( $C_{20}H_{38}O_2$ ), ethyl laurate ( $C_{16}H_{32}O_2$ ), ethyl linolenate ( $C_{19}H_{36}O_2$ ), ethyl stearate ( $C_{22}H_{44}O_2$ ), ethyl arachidate ( $C_{24}H_{48}O_2$ ), ethyl caprilate ( $C_{12}H_{24}O_2$ ), ethyl caprate ( $C_{14}H_{28}O_2$ ), ethyl caproate ( $C_{10}H_{20}O_2$ ), ethyl butyrate ( $C_8H_{16}O_2$ ), triacetin ( $C_{21}H_{40}O_6$ ), alpha tocopherol ( $C_{55}H_{104}O_2$ ), beta tocopherol ( $C_{55}H_{104}O_2$ ), delta tocopherol ( $C_{55}H_{104}O_2$ ), gamma tocopherol ( $C_{55}H_{104}O_2$ ), benzyl alcohol ( $C_7H_8O$ ), benzyl benzoate ( $C_{15}H_{14}O_2$ ), methylphenol ( $C_7H_8O$ ), di-n-butyl sebacate ( $C_{26}H_{50}O_4$ ), diethylphthalate ( $C_{16}H_{14}O_4$ ), glyceryl monooleate ( $C_{38}H_{74}O_4$ ), lecithin, medium chain triglycerides, mineral oil, petrolatum, and liquid paraffines.

5. Composition according to one of the claims 1 to 3, characterized in that the hydrophobic liquid is a vegetal oil preferably selected from the group of:

canola oil, corn oil, cottonseed oil, peanut oil, sesame oil, castor oil, and soybean oil.



6. Composition according to one of the claims 1 to 5, characterized in that said first and second component correspond together to 0,001 to 90,000 volume-% of the total weight of the three components together.

7. Composition according to claim 6, characterized in that said first and second component correspond together to 0,1 to 80,0 volume-% of the total weight of the three components together.

8. Composition according to one of the claims 1 to 7, characterized in that said third component corresponds to 10 to 90 volume-% of the total weight of the three components together.

9. Composition according to claim 8, characterized in that said third component corresponds to 20 to 80 volume-% of the total weight of the three components together.

10. Composition according to one of the claims 1 to 9, characterized in that it is obtained by combining 40 to 70 volume-% of said first and second component with 30 to 60 volume-% of said third component.

11. Composition according to one of the claims 1 to 10, characterized in that it has a CaP molar ratio comprised between 1,0 and 20,0.

12. Composition according to claim 11, characterized in that it has a CaP molar ratio comprised between 1,0 and 2,0.

13. Composition according to claim 12, characterized in that the calcium-containing cement paste has a CaP molar ratio comprised between 1,0 to 1,67.

14. Composition according to claim 13, characterized in that the calcium-containing cement paste has a CaP molar ratio comprised between 1,45 to 1,60.

15. Composition according to one of the claims 1 to 14, characterized in that said first component comprises calcium sulphate hemihydrate  $[\text{CaSO}_4 \cdot 1/2\text{H}_2\text{O}]$ , calcium pyrophosphate  $[\text{Ca}_2\text{P}_2\text{O}_7]$ , calcium carbonate  $[\text{CaCO}_3]$ , monocalcium phosphate monohydrate  $[\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}]$ , monocalcium phosphate  $[\text{Ca}(\text{H}_2\text{PO}_4)_2]$ , anhydrous dicalcium phosphate  $[\text{CaHPO}_4]$ , dicalcium phosphate dihydrate  $[\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}]$ , octocalcium phosphate  $[\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O}]$ , alpha-tricalcium phosphate  $[\text{alpha-Ca}_3(\text{PO}_4)_2]$ , beta-tricalcium phosphate  $[\text{beta-Ca}_3(\text{PO}_4)_2]$ , hydroxyapatite  $[\text{Ca}_5(\text{PO}_4)_3\text{OH}]$ , tetracalcium phosphate  $[\text{Ca}_4(\text{PO}_4)_2\text{O}]$ , calcium-deficient hydroxyapatite  $[\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}]$ , fluoroapatite  $[\text{Ca}_5(\text{PO}_4)_3\text{F}]$ , amorphous calcium phosphate, oxyapatite  $[\text{Ca}_{10}(\text{PO}_4)_6\text{O}]$ , calcium oxide and calcium hydroxide  $[\text{Ca}(\text{OH})_2]$  or a mixture of some or all of them.

16. Composition according to one of the claims 1 to 15, characterized in that said second component further comprises sulphuric acid [H<sub>2</sub>SO<sub>4</sub>], phosphoric acid [H<sub>3</sub>PO<sub>4</sub>], citric acid or a mixture of them.

17. Composition according to one of the claims 1 to 16, characterized in that said second component further comprises an additive to control the cement setting time, said additive being either a liquid substance or a solid substance soluble in water.

18. Composition according to claim 17, characterized in that said additive comprises a substance chosen from the group of pyrophosphate, citrate, magnesium, orthophosphate or polyphosphate ions, amino acids, peptides or proteins.

19. Composition according to one of the claims 1 to 18, characterized in that said second component further comprises an additive to control the cement rheology

20. Composition according to claim 19, characterized in that said additive to control the cement rheology is a polymer.

21. Composition according to claim 20, characterized in that said polymer is a polysaccharide.

22. Composition according to claim 21, characterized in that said polysaccharide is chosen from the group of:

hydroxypropylmethyl cellulose [CAS registry number 9004-65-3], hydroxypropylmethyl cellulose phthalate [CAS registry number 9050-31-1], hydroxyethyl cellulose [CAS registry number 9004-62-0], hydroxypropyl cellulose [CAS registry number 9004-64-2], tragacanth gum [CAS registry number 9000-65-1], sodium alginate [CAS registry number 9005-38-3], methyl cellulose [CAS registry number 9004-67-5], xanthan gum [CAS registry number 11138-66-2], hyaluronic acid [CAS registry number 9004-61-9], chitosan [CAS registry number 9012-76-4].

23. Composition according to claim 20, characterized in that said polymer is chosen from the group of:  
polyvinyl alcohol or propylene glycol alginate.

24. Composition according to one of the claims 1 to 23, characterized in that said second component further comprises a polymer to sterically stabilize the first component, preferably polyacrylic acid.

25. Composition according to claim 24, characterized in that said polymer is a polyacrylic acid.

26. Composition according to one of the claims 1 to 25, characterized in that the setting time of the cement upon mixing of said three components is comprised between 1 and 600 minutes.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 99/00684

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61L24/02 A61L27/02 A61L27/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 1988-311471 XP002116821 & JP 63 229058 A (OSHIMA Y), 22 September 1988 (1988-09-22) abstract	1,2,4, 13, 15-19, 21-23, 41,42, 45,47
X	PATENT ABSTRACTS OF JAPAN vol. 017, no. 413 (C-1092), 3 August 1993 (1993-08-03) & JP 05 085914 A (OSAKA CEMENT CO LTD), 6 April 1993 (1993-04-06) abstract	1-3,13, 22,23



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

5 October 1999

Date of mailing of the international search report

13/10/1999

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/00684

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 538 913 A (NITTA GELATIN KK) 28 April 1993 (1993-04-28) tables 1,3,4 claim 1 ---	1,4-28, 42,45-47
X	US 4 439 420 A (MATTEI FRANK V ET AL) 27 March 1984 (1984-03-27) claims column 3, line 50 - line 61 ---	1-8,16, 17,21-24
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A	US 4 959 104 A (IINO SHINJI ET AL) 25 September 1990 (1990-09-25) claims 1,6 ---	1,47
A	DATABASE WPI Derwent Publications Ltd., London, GB; AN 1990-280098 XP002116822 & JP 02 198560 A (NGK SPARK PLUG CO LTD), 7 August 1990 (1990-08-07) abstract ---	1
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A	US 5 681 873 A (TIPTON ARTHUR J ET AL) 28 October 1997 (1997-10-28) claims ---	1
A	US 4 322 398 A (REINER ROLAND ET AL) 30 March 1982 (1982-03-30) column 2, line 31 - line 49 example 4 claims -----	1

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/00684

### Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see further information

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/00684

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